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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,625	06/30/2003	Hiroyuki Asako	Q76266	9860

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,625	ASAKO ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *15-20,22 and 25-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,21,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/26/04 & 1/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment filed on June 30, 2003, amending claims 12-13, 15, 17 and 20 and adding claims 23-33, has been entered.

Claims 1-33 are pending. Claims 15-20, 22 and 25-33 are withdrawn. Claims 1-14, 21 and 23-24 are under consideration.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-14, 21 and 23-24) in the reply filed on November 23, 2005 is acknowledged.

Claims 15-20, 22 and 25-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 23, 2005.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Information Disclosure Statement

The information disclosure statements (IDS) submitted on February 26, 2004 and January 5, 2004 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

Claims 2-14 and 23-24 are objected to because of the following informalities: Claims 2-14 and 23-24 are objected for improper grammar. The claims should recite "The" instead of "A" in line 1 since said claims are all dependent claims. Appropriate correction is required.

Claim 8 is objected to because of the following informalities: Claim 8 is objected for improper grammar. The claim recites the word "by" instead of "with" in line 2 which alters the overall meaning. Appropriate correction is required.

Claim 21 is objected to because of the following informalities: Claim 21 is objected for improper grammar. The claim should recite "comprising" or "which comprises" instead of "comprises" in line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-14 and 23-24 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a non-statutory subject matter.

Claims 1-14 and 23-24, as written, do not sufficiently distinguish over polypeptides as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring

products, such as being "isolated". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified", for example, as taught by the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and claims 3-14 and 23-24 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 recite the term "having". The metes and bounds of this term in the context of the above claims are not clear to the Examiner. It is not clear to the Examiner whether reductase consists of substitutions at position 54 and/or 104 or comprises of substitutions at position 54 and/or 104 because the term "having" in transitional phrases does not create a presumption that the body of the claim is open (See MPEP 2111.03). A perusal of the specification did not provide the Examiner with a specific definition for the above term. As applicants have not provided a definition for the above term, Examiner has interpreted the claims broadly to mean that a reductase having substitutions at position 54 and/or 104 is a reductase "comprising" substitutions at position 54 and/or 104. Examiner requests clarification of the above phrase.

Claims 1-2 and claims 3-14 and 23-24 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 recite the phrase "reductase comprising ..an amino acid sequence of SEQ ID NO:1". The metes and bounds of this phrase in the context of the above claims are not clear to the Examiner. It is not clear to the Examiner if the "reductase" is a variant of SEQ ID NO:1 or if the reductase indeed has the same amino acid sequence of SEQ ID NO:1. If the latter is true, since the reductase must have the amino acid sequence of SEQ ID NO:1, said reductase can not have any amino acid substitutions or modifications. Examiner requests clarification of the above phrase and suggests amending the claim by replacing "an" with "the" in the above phrase.

Claims 3-4 and claims 6-13 and 23-24 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 recite the limitation "said single" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites the phrase "selectivity of said enzyme". The metes and bounds of this phrase are not clear to the Examiner. A perusal of the specification did not provide the Examiner with a specific definition for the above phrase. Therefore, it is not clear to the Examiner either from the specification or from the claim as to what specific "selectivity", such as substrate specificity, selectivity towards an optimum pH, temperature, etc, of the enzyme are encompassed in said phrase. Examiner requests clarification of the above phrase.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 recites the phrase "selectivity of said enzyme is improved". The metes and bounds of the phrase in the context of the above claim are not clear to the Examiner. It is not clear to the Examiner as to how much of an increase in the "selectivity" the enzyme is considered as "improved" by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition in terms of numerical value, those skilled in the art would be unable to conclude if "selectivity" of the enzyme is "improved". Examiner requests clarification of the above phrase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 21 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-14, 21 and 23-24 are drawn to a reductase which is a variant of SEQ ID NO:1 comprising substitutions at positions 54, 104, 245 and 271 and having further deletions, substitutions or addition of an amino acid or acids and a method of modifying an enzyme by substituting at least one single amino acid at amino acid positions 54 and 104 of EQ ID NO:1. The claims encompass a variant reductase of SEQ ID NO:1 comprising amino acids not limited to only substituting residues at position 54, 104, 245 and 271 with a single amino acid, but comprising modifying any amino acid in SEQ ID NO:1 with a single or multiple substitutions, deletions or additions. Therefore, the claims are drawn to a genus of reductase having any structure and a method of modifying SEQ ID NO:1 that results in a genus of enzymes having any structure. The specification only describes a reductase which is a variant of SEQ ID NO:1 consisting of single amino acid substitutions at positions 54, 104, 254 and 271 and a method of making such variant. However, this one example is not enough to describe the structure and more importantly do not constitute a representative number of species to describe the whole genus and there is no evidence on the record of the relationship between the structure of the claimed variant and the structure of any or all mutants, variants or recombinants of SEQ ID NO:1. Therefore, the specification fails to describe

the structure or even a representative number of species of the genus comprising variants of SEQ ID NO:1.

Claim 21 is drawn to a method of modifying SEQ ID NO:1 which results in an enzyme having improved "selectivity", but having any function, no function or unknown function. Therefore, many functionally unrelated polypeptides encompassed within the scope of claimed method. The genus of these polypeptides comprise a large variable genus with the potentiality of encompassing many different polypeptides having different structure and activity or no activity. The specification only describes a variant of SEQ ID NO:1 having reductase activity. The specification fails to describe additional representative species of the polypeptides by any identifying characteristics or properties of the polypeptides, for which no predictability of function is apparent. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1-14, 21 and 23-24.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-14, 21 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a reductase which is a variant of SEQ ID NO:1 consisting of amino acid substitutions at positions 54, 104, 254 and 271 of SEQ ID NO:1 and a method of making such variant, does not reasonably provide enablement for a method of modifying any amino acids of SEQ ID NO:1 or a variant reductase obtained from said method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-14, 21 and 23-24 are drawn to a reductase which is a variant of SEQ ID NO:1 comprising substitutions at positions 54, 104, 245 and 271 and having further deletions, substitutions or addition of an amino acid or acids and a method of modifying an enzyme by substituting "at least" one single amino acid at amino acid positions 54 and 104 of EQ ID NO:1. The claims encompass a method of modifying the reductase of SEQ ID NO:1 by changing any number of amino acids not limited to only substituting residues 54, 104, 245 and 271 with a single amino acid and a method of making such

enzyme, but modifying any amino acids of SEQ ID NO:1 with a single or multiple substitutions, deletions or additions. Therefore, the claims are drawn to a method of modifying any amino acids of SEQ ID NO:1 which results in variants having any structure and variants of SEQ ID NO:1 having any structure.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides and polypeptides encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a The specification only describes a reductase which is a variant of SEQ ID NO:1 consisting of single amino acid substitution at positions 54, 104, 254 and 271 and a method of making such variant.

It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides and improve selectivity of SEQ ID NO:1 by modifying any amino acids other than modifying the reductase of SEQ ID NO:1 with single amino acid substitutions at positions 54, 104, 254 and 271. The specification provides no guidance with regard to the making of other variants and mutants or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the

claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claim, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass modifying any amino acids in SEQ ID NO:1 and variant reductase that result from such modifications, because the specification does not establish: (A) regions of the polypeptide structure, other than a substitution at positions 54, 104, 254 and 271 in SEQ ID NO:1, which may be modified without affecting reductase activity; (B) specific amino acids in the polypeptide structure which may be modified resulting in improved selectivity; (C) the general tolerance of reductase to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (E) the specification

provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Claim 21 also broadly encompass a method of making variants, mutants and recombinants having reductase activity and polypeptides having any function or having no function. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The function of a polypeptide cannot be predicted from its structure and the specification does not teach how to use polypeptides having any function or having no activity. The quantity of experimentation in this area is extremely large since there is significant variability in the activity of the polynucleotides in the claims. It would require significant study to identify the actual function of the encoded polypeptides and identifying a use for the encoded polypeptide would be an inventive, unpredictable and difficult undertaking. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The art is extremely unpredictable with regard to protein function in the absence of realizable information regarding its activity. Even very similar proteins may have every different functions. In the current case, where no specific information is known regarding the function, it is entirely unpredictable what function and activity will be found for the protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the encoded polypeptides.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any or all variants of SEQ ID NO:1 and methods of making such variants. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of variants of SEQ ID NO:1 having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-14, 21 and 23-24 of this application conflict with claims 1-8, 15 and 17-18 of Application No. 10/608,533. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and

sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claims 1-14, 21 and 23-24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-8, 15 and 17-18 of copending Application No. 10/608,533. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Claims 1-14, 21 and 23-24 of the instant application and claims 1-8, 15 and 17-18 of the referenced application are both drawn to a reductase which is a variant of SEQ ID NO:1 comprising substitutions at positions 245 and 271 of SEQ ID NO:1 and a method of making such variants. The reductase of SEQ ID NO:1 of the instant application is 100% identical to the reductase of SEQ ID NO:1 of 10/608,625.

Claims 1-14, 21 and 23-24 of the instant application are drawn to a variant of SEQ ID NO:1 comprising substitutions at positions 245 and/or 271 of SEQ ID NO:1 and a method of making such variant. Claims 1-8, 15 and 17-18 of 10/608,625 are also drawn to a variant of SEQ ID NO:1 comprising substitutions at positions 245 and/or 271 of SEQ ID NO:1 and a method of making such variant. Therefore, the conflicting claims are not patentably distinct from each other.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Manjunath Rao
Primary Patent Examiner 1652